Preclinical Safety Assessment for Monoclonal Antibodies for BEID

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The opinions expressed by Dr. Ghantous in this presentation do not reflect official support or endorsement by the Food and Drug Administration

Where are Monoclonal antibodies regulated?

Oncology: Drugs, Biologics, Medical Imaging & Hematology

ODE I: Cardiovascular & Renal, Neurology, Psychiatry

ODE II: Pulmonary & Allergy, Metabolism & Endocrinology, Analgesics, Anesthetics & Rheumatology

ODE III: Reproductive & Urology, Gastroenterology, Dermatology & Dental

OAMP: Anti-Infectives & Ophthalmology, Special Pathogens & Immunology, Antivirals

OTC: Monograph Staff, NDA Staff

Relevant Guidance Documents

- **ICH S6**

  Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (1997)
- **Points to consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use (CBER/1997)**
- **Other**

  - ICH M3 (Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals) (1997)

  - ICH S5A (Detection of Toxicity to Reproduction for Medicinal Products) (1994)

  - ICH S7A (Safety Pharmacology Studies for Human Pharmaceuticals) (2001)

Documents specific to the preclinical development of Biologics

ICH S6 – Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (1997)

- **Generated under the same ICH process as all other ICH safety documents**
- **Based on critical review of experience of FDA/CBER and industry**
- **Covers essentially all areas of preclinical safety assessment**

Documents specific to the preclinical development of Monoclonal antibodies

Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use (1997)

- **Product Manufacturing and testing**
- **Preclinical studies**
  - **Tissue cross-reactivity (*in vitro, in vivo)***
  - **Pharmacokinetics and pharmacodynamics**
  - **Appropriately designed toxicology study in a relevant species**
  - **Reproductive and developmental toxicity**
  - **Justification for choice of species**
- **Clinical studies**

Monoclonal antibodies Specific Concerns

- **Cross reactivity with target and non-target tissues in human and relevant species**
- **Immunogenicity in test animal species**
- **Conjugate and/or linker toxicity**
- **Stability *in vivo***

Tissue Cross Reactivity

Tissue cross-reactivity (*in vitro, in vivo)*

Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use (1997)

- **Human cells or tissues (3 unrelated human donors)**
- **Concentration (lowest mAb concentration that produces maximum (Plateau) binding to target antigen)**
- **Positive and negative Controls (adequacy of assay)**
- **Naked or conjugated antibody**
- **Different animal species**

Cross reactivity of mAb with non-target human tissues should dictate a comprehensive *in vivo* investigation in animals, when appropriate models are available.

ICH S6

- **Relevant vs. non relevant species**
- **Animal models of disease**
- **Immunogenicity testing and its implications**
- **Genotoxicity testing**
- **Chronic toxicity testing**
- **Carcinogenicity testing**
- **Preclinical study design**

General principles (ICH S6)

- **Sufficiently well-characterized products**
- **Rely on purification processes to remove impurities/contaminants**
- **Comparability of test material demonstrated throughout development**
- **Conventional approaches to toxicity studies often NOT appropriate to address unique issues**
- **GLP compliance**

Characterization of general toxicity (ICH S6)

Administration/Dose Selection

- **ROA, dosing regimen should mimic proposed clinical use**
- **Alternative routes/regimens acceptable in some cases**
- **Toxic dose & NOAEL desirable**
- **Multiples of human dose needed to determine adequate safety margins can vary with product class & clinical indication**

Animal species and model selection (ICH S6)

Standard toxicology paradigms often *not* adequate or appropriate

Use of *relevant* species

- **single relevant species with justification**
- **limited toxicology in a single "nonrelevant" species**

Alternative approaches

- **transgenic animals**
- **homologous proteins**
- **animal models of disease**

What do the guidance documents say?

ICH S6

"A relevant species is one in which the test material is pharmacologically active due to the expression of a receptor or an epitope (in the case of monoclonal antibodies)."

What do the guidance documents say?

ICH S6

"Safety evaluation programs should normally include two relevant species. However, in certain justifiable cases, one relevant species may suffice (e.g., when only one relevant species can be identified or where the biological activity of the biopharmaceutical is well understood)."

"Toxicity studies in non-relevant species may be misleading and are discouraged."

Single/Repeat dose toxicity studies (ICH S6)

- **Use *relevant* animal species**
- **Include TK, Ab measurement, recovery period**
- **Short-term clinical use/acute life-threatening disease = toxicology studies of up to 2 weeks duration**
- **Chronic use = toxicology studies up to 6 months duration**
- **Safety Pharmacology**

What do the guidance documents say?

ICH S7A (Safety Pharmacology Studies for Human Pharmaceuticals)

“For biotechnology-derived products that achieve highly specific receptor targeting, it is often sufficient to evaluate safety pharmacology endpoints as a part of toxicology and/or pharmacodynamic studies”

What do the guidance documents say?

ICH S7A

“For biotechnology-derived products that represent a novel therapeutic class and/or those products that do not achieve highly specific receptor targeting, a more extensive evaluation by safety pharmacology studies should be considered”

Characterization of specific toxicities (ICH S6)

Immunogenicity

Genotoxicity

Carcinogenicity

- **Need for studies determined case-by-case**
- **Based on product characteristics, clinical use**
- **No specific guidance; work with the Divisions to design studies to address specific safety questions as needed**

Repro/Developmental Toxicity

What do the guidance documents say?

ICH S5A (Detection of Toxicity to Reproduction for Medicinal Products)

"In choosing an animal species and strain for reproductive toxicity testing, care should be given to select a relevant model."

"If it can be shown - by means of pharmacological and toxicological data - that the species selected is a relevant model for the human, a single species can be sufficient."

What do the guidance documents say?

ICH S5A

“There is little value in using a second species if it does not show the same similarities to humans.”

Summary

- **Preclinical studies for Biologics (mAb) have no "set" study paradigm**
  - **Design and implementation must consider clinical indication, population, and product characteristics**
- **Traditional animal toxicology models may not be appropriate or feasible**
- **Often studies have to be "individualized" to address specific safety concerns**
- **Guidance documents recognize the need, and support a different testing strategy for biologics**
- **Early Communication with FDA**

Efficacy Testing for BEID The Animal Rule – What is it?

- **21 CFR 314.600-650 or 600.90-95**
- **FDA may approve a product…based upon data obtained in adequate and well-controlled animal trials**
  - **treat serious/life-threatening conditions caused by exposure to lethal or permanently disabling toxic chemical, biological, radiological, or nuclear substances**
  - **results from animal studies establish likely clinical benefit in humans**
  - **human efficacy trials are not feasible or ethical**

Why are these studies needed?

- **Human efficacy trials are not feasible or ethical**
  - **human efficacy studies would require "unreasonable risk"**
  - **exposure to toxic chemicals, radiation, infectious agents as "disease" inducing**
  - **exposure to chemical/drug/biologic with substantial toxicity, but potential for clinical benefit in disaster setting**
- **Animal data become the sole source or "proof" of efficacy**
- **Clinical data still needed for safety**

Why are these studies needed?

- **Already used (under IND) in various settings**
  - **Gulf War, Kosovo, 2001 Anthrax**
  - **treatment of radiation accidents**
  - **in response to 9/11 (burns)**
  - **anti-viral drugs for smallpox**
- **Only one drug approved under "Animal Rule" to date**
  - **pyridostigmine bromide for prophy against nerve agents (*i.e.* Soman)**

How are these studies designed?

- **Pivotal efficacy studies should be designed in conjunction with the clinical review team**
- **Elements to consider:**
  - **is the pathophysiology, mechanism of toxicity of the challenge substance (chemical, biological, radiological, or nuclear) well-understood?**
  - **does the selected animal model(s) mimic the anticipated situation in humans?**
    - **time to development of disease**
    - **spectrum of clinical signs, morbidity, mortality?**
  - **what is the route of exposure for the challenge agent?**
    - **how different is it from the "natural" ROE?**
  - **what is the endpoint for the animal study?**
    - **should be relevant to clinical benefit**

How are these studies designed?

- **Elements to consider, cont'd:**
  - **what is the indication for the label?**
  - **statistical considerations**
    - **number of animals/sex/group**
    - **powering for desired effect size**
  - **Pharmacokinetic/pharmacodynamic endpoints need to be incorporated**
    - **both animal and human data required**
    - **allow selection of an effective dose in humans**
  - **Studies expected to be in compliance with GLP regulations**

How are these studies designed?

- **What it all boils down to:**
  - **case-by-case, depending on challenge, therapeutic agents, animal models and relevance to humans**
  - **animal study endpoint(s) is related to desired benefit in humans**
  - **effect of the therapeutic in animals is “reasonably likely” to predict effect in humans**
  - **input from the clinical review team is invaluable**

Relevant Guidance Documents

- **Fed Reg 67:37988-37998 (2002)**
- **Guidance for Industry**
  - **Inhalational Anthrax (Post-Exposure): Developing Anti-Microbial Drugs**

Summary

- **“Animal Rule” efficacy studies are used to support approval when human studies are not feasible, or unethical**
  - **not an easy path to follow**
  - **use basically as a “last resort”**
- **Studies should be conducted with the same rigor as a clinical pivotal study(ies)**
  - **animal data are substituting for human experience**
  - **replicate findings in more than one species, model**
  - **GLP compliance is expected!**

Summary

- **Dose-selection for human efficacy relies on comparative T/K, P/K data in humans**
- **Safety data will still come from human experience**
- **Design and implementation of these studies requires dialog**
  - **between the FDA and the sponsor**
  - **between the clinical and pharm/tox review teams**
  - **initiate early in development program**